

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference DH/12725.6	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/CA 98/ 01010	International filing date (day/month/year) 29/10/1998	(Earliest) Priority Date (day/month/year) 31/10/1997
Applicant CENTRE DE RECHERCHE DU CENTRE HOSPITALIER .. et al		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ **Certain claims were found unsearchable** (see Box I).

2. ☐ **Unity of invention is lacking** (see Box II).

3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the **title**, ☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

Figure No. _____ ☐ as suggested by the applicant.

☐ None of the figures.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 98/01010

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are theoretically contained within the definition "proteasome inhibitor" of claims 1,10 and 14, the search had to be restricted on economic grounds to the general idea of the invention and to the compound explicitly mentioned in the description and in claims 6,11,15 (Art. 6 PCT; Guidelines Chapt.II.7 last sentence and Chapt.III,3.7). Claims searched completely: 6,11,12,15-17

Claims searched incompletely:

1-5,7-10,13,14,18-20

INTERNATIONAL SEARCH REPORT

International Application No

PC 98/01010

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WANG X ET AL: "Role of proteasomes in T cell activation and proliferation." JOURNAL OF IMMUNOLOGY, (1998 JAN 15) 160 (2) 788-801. JOURNAL CODE: IFB. ISSN: 0022-1767., XP002093372 United States see the whole document ---	1-6
P,X	HIRSCH T ET AL: "Proteasome activation occurs at an early, premitochondrial step of thymocyte apoptosis." JOURNAL OF IMMUNOLOGY, (1998 JUL 1) 161 (1) 35-40. JOURNAL CODE: IFB. ISSN: 0022-1767., XP002093373 United States see the whole document ---	10-17
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

15 February 1999

Date of mailing of the international search report

02/03/1999

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INTERNATIONAL SEARCH REPORT

International Application No

PC 98/01010

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	X. WANG ET AL.: "RAPAMYCIN INHIBITS PROTEASOME ACTIVATOR EXPRESSION AND PROTEASOME ACTIVITY" EUR. J. IMMUNOL., vol. 27, no. 11, November 1997, pages 2781-2786, XP002093374 see the whole document ---	1-5, 7-10, 13, 14, 17-20
P,X	WO 98 13061 A (CV THERAPEUTICS INC ;JOLY ALISON (US); KERWAR SURESH (US); LUM ROB) 2 April 1998 see abstract see page 1, line 1 - line 15 see page 7, line 9 - line 19 see page 25, line 15 - page 26, line 9; claims; examples 2,5 ---	1-5, 7-10, 13, 14, 17-20
X	WO 96 32105 A (HARVARD COLLEGE ;SCHREIBER STUART L (US); STANDAERT ROBERT F (US);) 17 October 1996 cited in the application see abstract see page 81, line 1 - page 93, line 34; claims; examples 5,6,12 ---	1-20
X	WO 96 13266 A (PROSCRIPT INC) 9 May 1996 see abstract see page 5, line 1 - page 6, line 8 see page 9, line 8 - page 10, line 2 see page 30, line 9 - page 44, line 18; claims ---	1-5, 7-10, 13, 14, 17
X	WO 95 24914 A (MYOGENICS INC) 21 September 1995 cited in the application see abstract see page 10, line 7 - page 11, line 18; claims ---	1-5, 7-10, 13
X	WO 94 17816 A (HARVARD COLLEGE ;DANA FARBER CANCER INST INC (US)) 18 August 1994 see abstract see page 3, line 1 - line 32 see page 11, line 6 - line 21 see page 16, line 1 - line 9 see claims --- -/--	1-5, 7-10, 13

INTERNATIONAL SEARCH REPORT

International Application No

PCT 98/01010

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MEYER S ET AL: "Cyclosporine A is an uncompetitive inhibitor of proteasome activity and prevents NF-kappaB activation." FEBS LETTERS, (1997 AUG 18) 413 (2) 354-8. JOURNAL CODE: EUH. ISSN: 0014-5793., XP002093375 Netherlands see the whole document ----	1-5, 7-10,13, 14,17-20
X	J.E.F. REYNOLDS: "MARTINDALE, THE EXTRA PHARMACOPOEIA" 1996, ROYAL PHARMACEUTICAL SOCIETY, LONDON XP002093381 see page 557 - page 562 "Cyclosporin" see page 598 - page 600 "Sirolimus (Rapamycin)", "Tacrolimus (FK-506)" ----	1-5, 7-10,13, 14,17
X	CUI H ET AL: "Proteasome regulation of activation-induced T cell death." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 JUL 8) 94 (14) 7515-20. JOURNAL CODE: PV3. ISSN: 0027-8424., XP002093376 United States see the whole document ----	1-5
X	GRISCAVAGE J M ET AL: "Inhibitors of the proteasome pathway interfere with induction of nitric oxide synthase in macrophages by blocking activation of transcription factor NF-kappa B." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 APR 16) 93 (8) 3308-12. JOURNAL CODE: PV3. ISSN: 0027-8424., XP002093377 United States cited in the application see the whole document ----	10,13, 14,16,17
X	CONNER E M ET AL: "Proteasome inhibition attenuates nitric oxide synthase expression, VCAM-1 transcription and the development of chronic colitis." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 SEP) 282 (3) 1615-22. JOURNAL CODE: JP3. ISSN: 0022-3565., XP002093378 United States see the whole document ----	10,13, 14,16,17

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/98/01010

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MANNING A.M. ET AL: "Transcription inhibitors in inflammation." EXPERT OPINION ON INVESTIGATIONAL DRUGS, (1997) 6/5 (555-567). REFS: 86 ISSN: 1354-3784 CODEN: EOIDER, XP002093379 United Kingdom see abstract see page 561, right-hand column, last paragraph - page 562, left-hand column, last paragraph -----	1-17
A	IMAJOH-OHMI S ET AL: "Lactacystin, a specific inhibitor of the proteasome, induces apoptosis in human monoblast U937 cells." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1995 DEC 26) 217 (3) 1070-7. JOURNAL CODE: 9Y8. ISSN: 0006-291X., XP002093380 United States cited in the application -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/98/01010

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9813061	A	02-04-1998	US 5834487 A AU 4495997 A	10-11-1998 17-04-1998
WO 9632105	A	17-10-1996	AU 5542396 A CA 2217817 A EP 0820283 A US 5756764 A	30-10-1996 17-10-1996 28-01-1998 26-05-1998
WO 9613266	A	09-05-1996	AU 4139896 A CA 2203936 A CN 1168633 A EP 0788360 A FI 971746 A JP 10510245 T NO 971929 A US 5780454 A ZA 9509119 A	23-05-1996 09-05-1996 24-12-1997 13-08-1997 06-06-1997 06-10-1998 12-06-1997 14-07-1998 27-05-1996
WO 9524914	A	21-09-1995	AU 682600 B AU 2228395 A CA 2185326 A EP 0804216 A FI 963602 A JP 9511501 T NO 963814 A US 5693617 A	09-10-1997 03-10-1995 21-09-1995 05-11-1997 04-11-1996 18-11-1997 14-11-1996 02-12-1997
WO 9417816	A	18-08-1994	AU 676721 B AU 6169194 A CA 2155554 A EP 0684829 A JP 8507754 T	20-03-1997 29-08-1994 18-08-1994 06-12-1995 20-08-1996